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Concurrent Sessions

Concurrent Session 1 – Management of Hepatitis B

I-14 Treatment of hepatitis B virus

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HBV was discovered in 1964 and HBV suppression by treatment started in late 1970 by Dr. Greenberg using Interferon. However, until 1998 when Dr. CL Lai reported one year experience of Lamivudine in N Engl J Med, the treatment of HBV has not become common practice. That time, I wrote critical comment on this article by Editorial in N Engl J Med (1998; 339: 114–5). Because the majority of the patients treated had infection more than thirty years or sometimes even fifty years. And only one year suppression is not obviously sufficient to change the natural course of HBV infection. Subsequently, very high resistance rate was noted in the Lamivudine treatment and long-term efficacy was blurred.

And now, experiences of three to five years of drug use were gathered and several drugs seem so far very safe and potential suppressor of HBV replication for long time. Now the question is raised how long it can continue to suppress HBV before the emergence of HBV resistant mutant. In my talk, I will compare the potency and durability of several drugs and emergency of resistant strains. In addition, I will address the validations of new APASL guideline by our own patients' data and on the Japanese experiences of the improvement of liver history, treated by nucleoside analogues for 3 years. We know envision the use of these drugs for longer than five years. I personally feel if these drugs can suppress longer than ten years, probably the natural course of HBV infection could be drastically changed in the majority of HBV carriers.

I-15 From the pathogenesis to the therapeutic strategy of chronic hepatitis B infection

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Chronic HBV infection is a severe public health problem in the world, especially in China and Asia-Pacific Area. Although some new drugs developed in the treatment of chronic hepatitis B, such as pegylated interferon, lamivudine, adefovir, entecavir and telbivudine, not all the patients benefit from them, especially the sustain response is not satisfied.

There are two main reasons for the HBV infection as an intractable disease. One is the HBV cccDNA, the template for the replication of virus, that no drugs have worked on it. Another is the immune tolerance or dysfunction of the host immune system on HBV. The final elimination of the HBV cccDNA depends upon the immune system, that is, the viral specific cytotoxic T lymphocyte (CTL) and cytokines contribute the sustain viral inhibition by inducing the apoptosis of the viral infected hepatocytes, and the exhaustion of the cccDNA reservoir by sustain inhibition of the viral replication. So, immune modulation treatment that can provoke the immune system will play a very important role in the control of HBV infection.

As the sustain HBV inhibition rely on the immune system, the immune modulatory agents should be considered as the main therapeutic strategy of chronic HBV infection, unfortunately, only interferon α including pegylated interferon will be used in the young patients with low level HBV DNA and elevated ALT, and Thymosin $\alpha 1$ can be one of candidate as a immunomodulatory agent. As the nucleos(t)ide acid has a strong potency of inhibiting the virus but no immunomodulatory effect, the combination with two type agents will be a potential strategy in the future. The development of new agents with immunomodulatory effect may change the outcome of chronic hepatitis B patients, but there is a long way to go.

Concurrent Session 2 – Bacterial infection

I-16 Prevalence of *dupA* of *Helicobacter pylori* strains isolated from Shanghai patients and its clinical implications

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Aims: To determine the prevalence of duodenal ulcer promoting (*dupA*) gene of *Helicobacter pylori* in patients with various gastroduodenal diseases in Shanghai and to explore the association between the gene and other putative virulence factors.

Methods: *H. pylori* were isolated from gastric biopsies of patients with chronic gastritis, duodenal ulcer (DU), gastric ulcer (GU), or non-cardia gastric carcinoma. The *dupA*, *cagA*, *vacA*, *iceA* and *babA2* genotypes were determined by polymerase chain reaction. Histological features of gastric mucosal biopsy specimens were graded based on the scoring system proposed by the updated Sydney system.

Results: Isolates from 360 patients including 133 with chronic gastritis, 101 with DU, 47 with GU, and 79 with non-cardia gastric carcinoma were examined. The *dupA* gene was detected in 35.3% (127/360) and the prevalence DU patients was significantly greater than that in gastric cancer or GU patients (45.5% vs. 24.1% and 23.4%, $P < 0.05$). Patients infected with *dupA*-positive strains had

higher scores for chronic inflammation compared to those with *dupA*-negative strains (2.36 vs. 2.24, p = 0.058). The presence of *dupA* was not associated with the *cagA*, *vacA*, *iceA* or *babA 2* genotypes.
Conclusions: In Shanghai the prevalence of *dupA* gene was highest in DU and inversely related to GU and gastric cancer both which are associated with corpus atrophy.

I-17 Antimicrobial susceptibility testing through EUCAST

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In order to categorise a bacterium as sensitive to an antibiotic, it is necessary to perform a phenotypic antimicrobial susceptibility test. Phenotypic AST systems need breakpoints to. categorise bacteria S, I or R. Breakpoints are best determined by breakpoint committees consisting of experts in the fields of clinical microbiology and infectious diseases. Both CLSI (formerly NCCLS in the USA) and EUCAST (the European Committee on Antimicrobial Susceptibility Testing) are well known breakpoint committees. The former is a commercial enterprise engaging the pharmaceutical industry and the profession whereas the EUCAST is organised by the European Centre for Disease Control, the European Medicines Evaluation Agency and the European Society for Clinical Microbiology and Infectious Diseases. EUCAST has harmonised breakpoints for Europe and acts as the EMEA breakpoint committee during the process of approval of new drugs.
EUCAST breakpoints are currently being introduced in automated systems for AST. The Phoenix from Becton Dickinson is already validated with EUCAST breakpoints and the Vitek2 from BioMerieux is to follow. A disk test based on Mueller Hinton agar and 108 cfu/mL inoculum is currently being developed by EUCAST.
New therapeutic traditions, dosage practices, new tools for setting breakpoints and most importantly new resistance mechanisms necessitates an evolutionary process for clinical breakpoints. EUCAST has an active process for reviewing and revising breakpoints.
EUCAST offers free documents on breakpoints, methods and interpretive criteria on its website (www.eucast.org) which also displays MIC- (and eventually zone diameter-) distributions of wild type bacteria on the website. These can be used for calibration of methods.

I-18 *Laribacter hongkongensis*: From discovery to complete genome sequence

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Despite extensive investigations, a microbiological cause cannot be found in about half of the patients with infectious disease. Throughout the years, scientists have spent tremendous efforts in looking for microorganisms associated with these "unexplained infectious disease syndromes". In 2001, we discovered *Laribacter hongkongensis* gen. nov. sp. nov., a facultative anaerobic, Gram-negative, S-shaped, urease-positive rod of the Neisseriaceae family, from blood and empyema thoracis of a patient with alcoholic cirrhosis. During the past seven years, we have documented that *L. hongkongensis* was associated with gastroenteritis and traveler's diarrhea and cases were found globally in patients who resided in or had recent travel histories to countries in Asia, Europe, America and Africa. We have found that freshwater fish is the reservoir and it was also found in drinking water reservoirs. We have cloned the beta-lactamase and tetracycline resistance genes and developed gene deletion and expression systems for *L. hongkongensis*. Due to the potential of its clinical importance and related ecology, important phenotypic characteristics and phylogenetic position, and the availability of genetic manipulation systems for downstream experiments, we sequenced the complete genome of *L. hongkongensis*, with the aim of achieving better understanding of its biology, mechanism of adaptation to different hosts, and virulence mechanisms.

I-19 Antibiotic resistance in gram-negative pathogens: Dealing with untreatable infections

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While resistant gram-positive pathogens such as MRSA and VRE have received a lot of attention especially in the US and Europe, there have been rising numbers of multi-resistant and even pan-drug resistant strains of gram-negative bacilli in particular Pseudomonas and Acinetobacter spp. These have posed tremendous challenges to the clinicians looking after patients especially in Asia and Southern Europe. With limited therapeutic options, a greater focus on prevention and control has resulted. We are also hampered by a lack of good data to explain the emergence of these pathogens and to understand the reasons for their spread to our vulnerable patients.

I-20 Two stage theory pathogenic mechanism of *Streptococcus suis*

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Streptococcus suis infections are enzootic in pigs where sporadic cases occur in humans. Since the first human case was recorded in 1968, only 250 cases have been reported globally through June 2005. The majority of the cases have resulted in meningitis often associated with hearing loss. During the period from July to August 2005, however, an explosive outbreak of 215 cases of human infection occurred in Sichuan Province, China. Sixty-one of the 215 (28%) patients presented an unusual streptococcal toxic shock like syndrome (STSLS) with high mortality (38 of 61; 62%) in previously healthy farmers. Both the clinical presentation and epidemiology features of the Sichuan outbreak had not previously been observed.
This outbreak was caused by a mutant *S. suis* named as sequence type 7 (ST7) using the multi-locus sequence typing method, the method of choice for addressing questions related to genotyping for epidemiological studies, population, and evolutionary biology. The ST7 strain caused a single case described from Hong Kong in 1996; then it emerged to cause a small outbreak in Jiangsu in 1998; and spread to cause the largest ever outbreak with severe shock in 2005.
It was found that the serum levels of IL-1β, IL-6, IL-8, IL-12, p70, IFN-γ and TNF-α, the inflammation cytokines, during the early phase of the disease were significantly elevated in patients with STSLS compared to those with meningitis only. And, the serum levels of pro-inflammatory cytokines were significantly higher in mice infected with the ST7 strain than in those infected with either the ST1 or ST25 strains.
Genome comparisons showed the ST1 strain had acquired 132 genomic islands, including 5 pathogenicity islands, and the "epidemic" strain ST7 had acquired an additional 5 genomic islands. Therefore, We proposed the intermediate virulent ST25 type evolved to become the highly pathogenic